EXPLANATION OF SOURCE OF NEW CLAIMS

Explanation of source of language used for the additional claims to add to claims 1 to 14 of US Serial No. 09/376, 487 Injectable Aqueous Dispersions of Propofol.

Deletions are in brackets, additions of new claim language are underlined, and the residual text from existing specification and claims 1-14 that is used to form these new, additional claims is in bold.

New additional claim 15 is derived from the pharmaceutical composition aspect of the text of the original claim 13 except for the additional words "an injectable" and "capable of substantially limiting or inhibiting the growth of microorganisms" which are taken (underlined) from the first paragraph of the "Summary" found on page 7 in the phrase:

> "an injectable aqueous dispersion of a water-insoluble matrix consisting of propofol and propofol-soluble agents, were capable of substantially limiting or inhibiting the growth of [certain]microorganisms and did not display the incidence of irritation at the injection site"

and the phrase: "**and causes little or no tissue-irritation at the site of injection**" taken from page 8 just before "Description of the Invention" in place of the phrase "**results in little or no tissue-irritation at the site of injection"** from original claim 1. The values of up to 7% of the propofol-soluble diluent and up to 4% for the surface stabilizing agent are in original claim 14.

15. [The method of reducing or substantially completely eliminating irritation upon injection of formulations containing propofol by administering] [a]**An injectable, stable, sterile, and antimicrobial aqueous dispersion** [of] comprising a **water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm capable of substantially limiting or inhibiting the growth of** [certain] **microorganisms consisting essentially of about 1% to about 15% of propofol** [as the active ingredient], **up to about 7% of a propofol-soluble diluent, and about 0.8% to about 4% of a surface stabilizing amphiphilic agent, and the aqueous phase** [of the composition consisting of] comprising **a pharmaceutically acceptable water-soluble polyhydroxy tonicity modifier, the** [composition] dispersion **being devoid of additional bactericidal or bacteriostatic**

preservative agents[, provided the ratio of propofol to diluent is about 1:4 to about 1:0.1 and the ratio of propofol to amphiphlic agent is about 1:0.8 to about 1:2.5, and the composition has a viscosity of from about 0.8 to about 15 centipoise] **and** [causes] causing **little or no irritation at the site of injection.**

The following additional claims 16, 17, and 18 are derived from original claim 13 except for the underlined section which identifies the antecedent "dispersion" of the additional claim 15.

16. The **dispersion** of claim 15 where **the** [ratio of] **propofol** [to] and **diluent** are present in the ratio of [is] **about 1:4 to about 1:0.1.**

17. The **dispersion** of claim 15 where **the** [ratio of] **propofol** [to] and **amphiphlic agent** are present in the ratio of [is] **about 1:0.8 to about 1:2.5.**

18. The **dispersion** of claim 15 that **has a viscosity of from about 0.8 to about 15 centipoise.**

The following claim (additional claim 19) is derived in part from original claim 3 in which the antecedent is now identified as the "dispersion of claim 15" rather than the "composition of claim 1". The claim further contains text "**saturated or unsaturated** taken from the specification on pages 9 to 10 under the heading "Composition" and the phrase "pharmaceutically acceptable" from the phrase "...[use] pharmaceutically acceptable [ingredients]" appearing on page 27 line 2.

19. The [composition] **dispersion** of claim [1]15 wherein **the propofol-soluble diluent is a pharmaceutically acceptable saturated or unsaturated synthetic or natural fatty acid, triglyceride thereof** [or other suitable ester] **or a mixture thereof.**

The following claim (additional claim 20) is derived in part from original claim 3 as above in which the antecedent is now identified as the "dispersion of claim 15" rather than the "composition of claim 1". The claim further contains text selected from the

specification on pages 9 to 10 under the heading "Composition" which text includes the following words:

> "... **one or more selected from** saturated or unsaturated fatty acid esters such as isopropyl myristate, cholesteryl oleate, ethyl oleate, squalene, squalane, alpha-tocopherol and/or derivatives of alpha-tocopherol, **esters or triglycerides of** either **medium chain and/or long chain fatty acids of synthetic or natural origin**. The natural triglycerides can be selected particularly from the vegetable or animal sources, e.g., pharmaceutically acceptable vegetable oils or fish oils. The latter are also known as omega-3 polyunsaturated oils. The lipophilic agents may also be considered propofol-soluble agents or diluents"

and also text selected on page 27 line 2 as above, i.e,

> "pharmaceutically acceptable" from the phrase
>
> "[use] pharmaceutically acceptable [ingredients]."

20. The [composition]**dispersion** of claim [1]15 wherein **the propofol-soluble diluent is one or more selected from pharmaceutically acceptable esters or triglycerides of medium chain and/or long chain fatty acids of synthetic or natural origin.**

The following claim (additional claim 21) is derived in part from original claim 3 as above in which the antecedent is now identified as the "dispersion of claim 15" rather than the "composition of claim 1". The claim further contains text selected from the specification on page 9 under the heading "Composition" which text includes the following words:

> "... **one or more selected from** saturated or unsaturated fatty acid esters such as **isopropyl myristate, cholesteryl oleate, ethyl oleate, squalene, squalane, alpha-tocopherol** and/or derivatives of alpha-tocopherol ..."

The claim further contains text selected from the specification on page 20, example 2, third paragraph, line 6: "Miglyol-810"

21. The [composition] **dispersion** of claim [1]15 wherein **the propofol-soluble diluent is one or more selected from isopropyl myristate, cholesteryl oleate, ethyl oleate, squalene, squalane, alpha-tocopherol,** and **Miglyol-810.**

The following claim (additional claim 20) is derived in part from original claim 3 as above in which the antecedent is now identified as the "dispersion of claim 15" rather than the "composition of claim 1". The claim further contains text selected from the specification on pages 9 to 10 under the heading "Composition" which text includes the following words:

> "... **one or more selected from** [saturated or unsaturated fatty acid esters such as isopropyl myristate, cholesteryl oleate, ethyl oleate, squalene, squalane, alpha-tocopherol and/or derivatives of alpha-tocopherol, esters or triglycerides of either medium chain and/or long chain fatty acids of synthetic or natural origin. The] **natural triglycerides** [can be selected particularly] **from** [the] **vegetable or animal sources,** [e.g.,] **pharmaceutically acceptable vegetable oils** [or] **fish oils**[. The latter are also known as] **omega-3 polyunsaturated** oils. The lipophilic agents may also be considered propofol-soluble agents or diluents"

and also text selected on page 27 line 2 as above, i.e,

> "pharmaceutically acceptable" from the phrase
>
> "[use] pharmaceutically acceptable [ingredients]."

22. The [composition] **dispersion** of claim [1]15 wherein **the propofol-soluble diluent is one or more selected from pharmaceutically acceptable natural triglycerides from vegetable or animal sources, pharmaceutically acceptable vegetable oils, and omega-3 polyunsaturated fish oils.**

The following claim (claim 23) is derived in part from original claim 3 as above in which the antecedent is now identified as the "diluent of claim 22" rather than the "composition of claim 1" and the "vegetable oil" is now defined as "soybean oil" taken from Table II on page 24.

23. The [composition] **diluent** of claim [1]22 wherein **the vegetable is soybean.**

The following claim (claim 24) is derived from original claim 6 as above in which the antecedent is now identified as the "dispersion of claim 15" rather than the "composition of claim 1".

24. The [composition] **dispersion** of claim [1]15 wherein **the propofol-soluble diluent is a mixture of medium-chain triglyceride and vegetable oil.**

The following claim (claim 25) is derived from original claim 7 as above in which the antecedent is now identified as the "diluent of claim 24" rather than the "composition of claim 1".

25. The [composition] **diluent** of claim [6]24 wherein **the ratio of medium-chain triglyceride to vegetable oil is from 1:3 to 3:1.**

The following claim (claim 26) is derived from original claim 8 as above in which the antecedent is now identified as the "dispersion of claim 15" rather than the "composition of claim 1".

26. The [composition]**dispersion** of claim [1]15 **wherein the water-insoluble matrix consists of a mixture of about 1% to about 15% of propofol** [as the active ingredient], **up to about 7% of a propofol-soluble diluent, and about 0.8% to about 4% of a surface stabilizing amphiphilic agent.**

The following claim (claim 27) is derived from original claim 9 as above in which the antecedent is now identified as the "dispersion of claim 15" rather than the "composition of claim 1".

27. The [composition]dispersion of claim [1]15 wherein **the water-insoluble matrix contains about 2% to about 10% of propofol.**

The following claim (claim 28) is an additional claim derived from the original claim 2 as above in which the antecedent is now identified as the "dispersion of claim 15" rather than the "composition of claim 1".

28. The [composition]**dispersion** of claim [1]15 **wherein the surface stabilizing amphiphilic agent is one or more natural or synthetic surface modifiers selected from ionizable or non-ionizable phospholipids or cholesterol or a mixture of these amphiphilic agents.**

The following claims (claim 29 and 30) are additional claims derived from page 10 second paragraph (below) and in which the antecedent is now identified as the "dispersion of claim 15" rather than the "composition of claim 1".

> "At the surface of the water-insoluble matrix are amphiphilic agents that stabilize the dispersion and are of possible importance in affecting the degree of local reaction on injection. Examples of such amphiphilic agents include **charged or uncharged phospholipids of natural sources**, *e.g.*, egg or soy lecithin, or **hydrogenated lecithin** (*e.g.*, phospholipon-90H or phospholipon-100H from Nattermann), or **synthetic phospholipids** such as phosphatidylcholines or phosphatidylglycerols, **pharmaceutically acceptable non-ionic surfactants** such as **poloxamers** (pluronic series of surfactants), **poloxamines** (tetronic series of surfactants), **polyoxyethylene sorbitan esters** (*e.g.*, Tween® series of surfactants), **cholesterol**, or other surface modifiers commonly used in pharmaceutical products, **or combinations of these surface modifiers**."

29. The [composition]**dispersion** of claim [1]15 wherein **the surface stabilizing amphiphilic agent is one or more charged or uncharged phospholipids of natural sources, hydrogenated lecithin, synthetic phospholipids, or poloxamers or poloxamines or polyoxyethylene sorbitan esters or combinations of these surface modifiers.**

30. The [composition]**dispersion** of claim [1]15 wherein **the surface stabilizing amphiphilic agent is a combination of cholesterol and one or more charged or uncharged phospholipids of natural sources, hydrogenated lecithin, or synthetic phospholipids.**

The following claim (claim 31) is an additional claim derived from the table on page 17 and from the middle paragraph on page 10 and in which the antecedent is now identified as the "dispersion of claim 15" rather than the "composition of claim 1".

31. The [composition]**dispersion** of claim [1]15 wherein **the surface stabilizing amphiphilic agent is Lipoid E80, or Lipoid EPC, or Lipoid SPC, or Lipoid SPC-3, or phospholipon-90H or phospholipon-100H.**

The following claim (claim 32) is an additional claim derived from the table on page 17 and from the middle paragraph on page 9 and from the footnote to table II on page 24,

and in which the antecedent is now identified as the "dispersion of claim 15" rather than the "composition of claim 1".

32. The [composition]**dispersion** of claim [1]15 wherein **the surface stabilizing amphiphilic agent is 1,2-dimristoyl-sn-glycero-3-phosphocholine**, or **1,2-dimristoyl-sn-glycero-3-[phospho-rac-(1-glycerol)]**, or **egg lecithin**, or **egg phosphatidylcholine**, or **soy phosphatidylcholine**, or **saturated soy phosphatidylcholine**, or **soy lecithin**, or **dimyristoylphosphatidylcholine**, or **dimyristoylphosphatidylglycerol.**

The following claims (claims 33, 34, and 35) are additional claims derived from original claim 2 as above in which the antecedent is now identified as the "dispersion of claim 15" rather than the "composition of claim 1".

33. The [composition]**dispersion** of claim [1]15 **that has a non-existent or minimum potential for hemolysis of human or animal blood.**

34. The [composition]**dispersion** of claim [1]15 where **irritation to the tissues at the site of injection is either non-existent or minimized.**

35. The [composition]**dispersion** of claim [1]15 that **elicits an anesthetic** or sedation **effect in warm-blooded animal and human subjects upon intravenous administration.**

The following claims (claims 36, 37, 38 and 39) are additional claims derived from page 10 third paragraph (below) and in which the antecedent is now identified as the "dispersion of claim 15" rather than the "composition of claim 1".

36. The [composition]**dispersion** of claim [1]15 wherein **the tonicity modifier is sucrose, dextrose, trehalose, mannitol, lactose, or glycerol.**

37. The [composition]**dispersion** of claim [1]15 wherein **the tonicity modifier comprises a mixture of sucrose, dextrose, trehalose, mannitol, lactose, or glycerol.**

38. The [composition]**dispersion** of claim [1]15 **that is isotonic with blood.**

39. The [composition]**dispersion** of claim [1]15 **that is suitable for intravenous injection.**

The following claim (claim 40) is an additional claim derived from original claim 10 as above in which the antecedent is now identified as the "dispersion of claim 15" rather than the "composition of claim 1".

40. The [composition]**dispersion** of claim [1]15 **that contains a pharmaceutically acceptable water-soluble polyhydroxy additive that provides an osmolality of about 250 to about 700 milliosmolal.**

The following claim (claim 41) is an additional claim derived from original claim 11 as above in which the antecedent is now identified as the "dispersion of claim 15" rather than the "composition of claim 1".

41. The [composition]**dispersion** of claim [1]15 wherein **the osmolality is about 300 to about 500 milliosmolal.**

The following claim (claim 42) is an additional claim derived from original claim 12 as above in which the antecedent is now identified as the "dispersion of claim 15" rather than the "composition of claim 1".

42. The [composition]**dispersion** of claim [1]15 wherein **the viscosity is from about 2 to about 5 centipoise.**

The following claim 43 is derived from the language on page 13 first paragraph headed by "Packaging and Sterilization".

> "The aqueous dispersion prepared by one of the above processes was filled into glass **vials** to about 70-90% volume capacity, purged with a generally inert atmosphere, for example nitrogen, and **sealed** with compatible stoppers and seals. The packaged novel propofol formulations were found generally to be stable pharmaceutically acceptable steam sterilization cycles"

43. A **sealed vial** containing the dispersion of claim 15.

The following claim 44 is a process claim where the text is taken in part from new claim 15 above and from the specification page 11 under "Method", last sentence on page 11:

> "...**the initial preparation of a lipophilic phase and an aqueous phase** which are then **mixed** ..."

and page 12 under **Premix Preparation**:

> "**Propofol, other lipophilic agents, and ampiphilic agents** were **mixed to prepare the lipophilic phase**. The dissolution process was accelerated by heating the mixture while mixing with a high-speed homogenizer. **The aqueous phase** was usually **a mixture of polyhydroxy compounds in water** and in some cases also contained well-dispersed phospholipid prepared using a high-speed homogenizer. The premix was prepared by adding the lipophilic phase to the aqueous phase **under agitation with a high-speed homogenizer** and the pH adjusted. All these operations were performed **under a generally inert atmosphere**, for example a nitrogen blanket, **and the temperature** was **controlled to minimize oxidation**"

and from page 12 under the heading "Homogenization"

> "The dispersions of the water insoluble matrix in aqueous medium were prepared by either of several homogenization methods. For example, **dispersions** were **prepared by high pressure homogenization of the premix** *e.g.*, by utilizing a Rannie MINI-LAB, type 8.30H Homogenizer, APV Homogenizer Division, St. Paul, MN. Alternatively, the dispersions were **made by microfluidization of the premix** with a Microfluidizer M110EH (Microfluidics, Newton, MA). The temperature of the process-fluid rises rapidly because of homogenization at a high pressure. In some cases high-pressure homogenization at high temperatures (homogenizer inlet temperature above about 30°C) resulted in a dispersion with a tendency to suffer from phase separation. Therefore, the effluent of the homogenizer was cooled to maintain an acceptable temperature at the inlet of the homogenizer"

and from page 13 under the heading "Packaging and Sterilization"

> "**The aqueous dispersion** prepared by one of the above processes **was filled into glass vials** to about 70-90% volume capacity, **purged with a generally inert atmosphere,** for example nitrogen, **and sealed with compatible stoppers and seals.** The packaged novel propofol formulations were found generally to be stable pharmaceutically acceptable steam sterilization cycles"

44. A process for preparing an injectable, stable, sterile, and antimicrobial aqueous dispersion of water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm capable of substantially limiting or inhibiting the growth of microorganisms consisting essentially of about 1% to about 15% of propofol, up to about 7% of a propofol-soluble diluent, and about 0.8% to about 4% of a surface stabilizing amphiphilic agent, and the aqueous phase comprising a pharmaceutically acceptable water-soluble polyhydroxy tonicity modifier, the composition being devoid of additional bactericidal or bacteriostatic preservative agents and causes little or no irritation at the site of injection comprising the initial preparation of a premix of a lipophilic phase and an aqueous phase mixed under agitation with a high-speed homogenizer under a generally inert atmosphere and the temperature controlled to minimize oxidation wherein propofol, other lipophilic agents, and ampiphilic agents are mixed to prepare the lipophilic phase and the aqueous phase is a mixture of polyhydroxy compounds in water and wherein a dispersion is prepared by high pressure homogenization of the premix or made by microfluidization of the premix, the aqueous dispersion filled into glass vials, purged with a generally inert atmosphere, and sealed with compatible stoppers and seals.